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(54) Title: NEW NUCLEOTIDE SEQUENCES (57) Abstract The present invention relates to a nucleic acid molecule encoding a GABA _B receptor, or a functionally equivalent modified form thereof, said receptor being selected from the group consisting of human and canine GABA _B receptors.			
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NEW NUCLEOTIDE SEQUENCES

TECHNICAL FIELD

- 5 The present invention relates in particular to nucleic acid molecules encoding GABA_B receptors, and to methods for screening for compounds which are inhibitors of transient lower esophageal sphincter relaxations (TLESR), said methods comprising the use of a nucleic acid molecule encoding a GABA_B receptor.

10

BACKGROUND ART

GABA_B receptors

- 15 GABA (4-aminobutanoic acid) is an endogenous neurotransmitter in the central and peripheral nervous systems. Receptors for GABA have traditionally been divided into GABA_A and GABA_B receptor subtypes. GABA_B receptors (for a review see Kerr, D.I.B. and Ong, J. (1995) Pharmac. Ther. vol. 67, pp.187-246) belong to the superfamily of G-protein coupled receptors. GABA_B receptor agonists are described as being of use in the
- 20 treatment of CNS disorders, such as muscle relaxation in spinal spasticity, cardiovascular disorders, asthma, gut motility disorders such as irritable bowel syndrome and as prokinetic and anti-tussive agents. GABA_B receptor agonists have also been disclosed as useful in the treatment of emesis (WO 96/11680).
- 25 The cloning of the rat GABA_B receptors GABA_BR1a (SEQ ID NOS: 44 and 45) and GABA_BR1b (SEQ ID NOS: 46 and 47) is disclosed by Kaupmann et al. (1997) Nature, vol. 386, 239-246. The mature rat GABA_BR1b differed from GABA_BR1a in that the N-terminal 147 residues were replaced by 18 different residues. It was presumed that the rat GABA_BR1a and -b receptor variants are derived from the same gene by alternative
- 30 splicing.

The cloning of the human GABA_B receptor GABA_BR1b is disclosed in WO 97/46675.

Reflux

- 5 In some humans, the lower esophageal sphincter (LES) is prone to relaxing more frequently than in other humans. As a consequence, fluid from the stomach can pass into the esophagus since the mechanical barrier is temporarily lost at such times, an event hereinafter referred to as "reflux".
- 10 Gastro-esophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease. Current therapy has aimed at reducing gastric acid secretion, or by reducing esophageal acid exposure by enhancing esophageal clearance, lower esophageal sphincter tone and gastric emptying. The major mechanism behind reflux has been considered to depend on a hypotonic lower esophageal sphincter. However, recent research (e.g.
- 15 Holloway & Dent (1990) Gastroenterol. Clin. N. Amer. 19, 517-535) has shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESR), i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal in patients with GERD. Consequently, there is a need for compounds which reduce the incidence of TLESR and thereby prevent reflux.

20

DISCLOSURE OF THE INVENTION

- In the applicants' earlier patent application WO 98/11885, filed on 15 September 1997, it is
- 25 disclosed that GABA_B receptor agonists can be used to reduce the incidence of transient lower esophageal sphincter relaxations (TLESR).

- The present invention provides nucleic acid molecules encoding human and canine GABA_B receptors. These nucleic acid molecules will make possible the screening for
- 30 compounds which are agonists or antagonists of GABA_B receptors, e.g. compounds which are inhibitors of transient lower esophageal sphincter relaxations (TLESR).

Consequently, in a first aspect, the present invention provides a nucleic acid molecule encoding a GABA_B receptor, or a functionally equivalent modified form thereof, said receptor being selected from the group consisting of human and canine GABA_B receptors.

5 In preferred forms of the invention, the said nucleic acid molecule encodes the human GABA_B receptor 1a (SEQ ID NOS: 48 and 49), 1b (SEQ ID NOS: 50 and 51), 1c (SEQ ID NOS: 54 and 55) or 1d (SEQ ID NOS: 56 and 57); or the canine GABA_B receptor 1a (SEQ ID NOS: 52 and 53) or 1c (SEQ ID NOS: 58 and 59). Accordingly, the invention furthermore provides a nucleic acid molecule selected from:

- 10 (a) nucleic acid molecules comprising a nucleotide sequence set forth as SEQ ID NO: 48, 50, 52, 54, 56 or 58;
- (b) nucleic acid molecules comprising a nucleotide sequence capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence complementary to the polypeptide coding region of a DNA molecule as defined in (a); and
- 15 (c) nucleic acid molecules comprising a nucleotide sequence which is degenerate as a result of the genetic code to a nucleotide sequence as defined in (a) or (b).

Furthermore, the invention provides nucleic acid molecules of genomic origin encoding human GABA_B receptors (SEQ ID NOS: 60 and 61) as well as nucleic acid molecules (set
20 forth as SEQ ID NO: 70, 72, 74, 76, 78, 80, 82, 84) encoding additional isoforms of the human GABA_B receptor which isoforms can be shown to be generated by alternative splicing.

It should thus be understood that the nucleic acid molecule according to the invention is
25 not to be limited strictly to molecules comprising the sequences set forth as SEQ ID : 48, 50, 52, 54, 56 or 58. Rather the invention encompasses nucleic acid molecules carrying modifications like substitutions, small deletions, insertions or inversions, which nevertheless encode proteins having substantially the biochemical activity of the GABA_B receptors according to the invention. Included in the invention are consequently nucleic
30 acid molecules, the nucleotide sequence of which is at least 95% homologous, preferably at least 96%, 97%, 98% or 99% homologous, with the nucleotide sequence shown as SEQ ID NO: 48, 50, 52, 54, 56 or 58 in the Sequence Listing.

The term "stringent hybridization conditions" is known in the art from standard protocols (e.g. Current Protocols in Molecular Biology, editors F. Ausubel et al., John Wiley and Sons, Inc. 1994) and could be understood as as stringent or more stringent than those
5 defined by e.g. hybridization to filter-bound DNA in 0.5 M NaHPO₄, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at +65°C, and washing in 0.1xSSC / 0.1% SDS at +68°C.

Included in the invention is also a nucleic acid molecule which nucleotide sequence is degenerate, because of the genetic code, to a nucleic acid of the present invention and more
10 particularly to one of the nucleotide sequences set forth as SEQ ID NOs: 48, 50, 52, 54, 56 and 58. A sequential grouping of three nucleotides, a "codon", codes for one amino acid. Since there are 64 possible codons, but only 20 natural amino acids, most amino acids are coded for by more than one codon. This natural "degeneracy", or "redundancy", of the genetic code is well known in the art. It will thus be appreciated that the nucleic acid
15 sequences shown in the Sequence Listing is only an example within a large but definite group of nucleic acid sequences which will encode the polypeptide as described above.

In a further aspect, the invention provides a recombinant polypeptide encoded by a nucleotide sequence of the present invention, encoding a GABA_B receptor. In preferred
20 forms of the inventions, the said polypeptide comprises an amino acid sequence set forth as SEQ ID NO: 49, 51, 53, 55, 57, 59, 71, 73, 75, 77, 79, 81, 83 or 85 in the Sequence Listing. However, polypeptides of the present invention are not to limited to those having an amino acid sequence identical with one of SEQ ID NOs: 49, 51, 53, 55, 59, 71, 73, 75, 77, 79, 81, 83 or 85 in the Sequence Listing. Rather the invention encompasses polypeptides carrying
25 modifications such as substitutions, small deletions, insertions or inversions, which polypeptides nevertheless have substantially the biological activities of the GABA_B receptor. Included in the invention are consequently polypeptides, the amino acid sequence of which is at least 95% homologous, preferably at least 96%, 97%, 98% or 99% homologous, with one of the amino acid sequences described by SEQ ID NOs: 49, 51, 53,
30 55, 57 59, 71, 73, 75, 77, 79, 81, 83 and 85 in the Sequence Listing.

Included in the invention are polypeptides of the present invention which have been post-translationally modified, e.g. by cleavage of an N-terminal signal sequence which can be e.g. 1 to 25 amino acids long.

- 5 In yet another aspect, the invention provides a vector transformed with a nucleic acid molecule of the present invention. The said vector can e.g. be a replicable expression vector which carries and is capable of mediating the expression of a nucleic acid molecule according to the invention. In the present context the term "replicable" means that the vector is able to replicate in a given type of host cell into which it has been introduced.
- 10 Examples of vectors are viruses such as bacteriophages, cosmids, plasmids and other recombination vectors. Nucleic acid molecules are inserted into vector genomes by methods well known in the art.

- Included in the invention is also a cultured host cell harbouring a vector according to the invention. Such a host cell can be a prokaryotic cell, a unicellular eukaryotic cell or a cell derived from a multicellular organism. The host cell can thus e.g. be a bacterial cell such as an *E. coli* cell; a cell from a yeast such as *Saccharomyces cerevisiae* or *Pichia pastoris*, or a mammalian cell. The methods employed to effect introduction of the vector into the host cell are standard methods well-known to a person familiar with recombinant DNA
- 15 methods.
- 20

- A further aspect of the invention is a process for production of a GABA_B receptor polypeptide according to the invention, said process comprising culturing a host cell as defined above under conditions whereby the said polypeptide is produced, and recovering
- 25 the said polypeptide.

- A further important aspect of the invention is a method for the screening of compounds which are inhibitors of transient lower esophageal sphincter relaxations (TLESR), said method comprising the use of a nucleic acid molecule encoding a GABA_B receptor. The said nucleic acid molecule encoding a GABA_B receptor can e.g. be one of the nucleic acid molecules according to the invention encoding human or canine GABA_B receptors.
- 30
- However, it should be understood that this aspect of the invention is not limited to the use

of the said human and canine GABA_B receptors, but rather encompasses the use of any GABA_B receptor for screening for compounds which are inhibitors of transient lower esophageal sphincter relaxations.

- 5 In yet another important aspect, the invention provides a method for the screening of compounds which are agonists or antagonists to a GABA_B receptor, said method comprising the use of a nucleic acid molecule, according to the invention, encoding human or canine GABA_B receptors.

10 **Brief Description of the Drawings**

Figure 1: Map of the human GABA_B receptor gene.

The exon/intron organisation is shown. Exons are indicated as solid boxes numbered 1-23.

- 15 The part of intron 5 that is retained together with exon 6 giving rise to GABA_B receptor 1b is indicated as an open box.

Figure 2: Expression of human GABA_B receptor 1b isoform in transfected C127 cells.

20

Western blot analysis of transfected C127 cells using a polyclonal anti-human GABA_B receptor antibody. Lane 1: Untransfected C127 whole cell lysate. Lanes 2-7: Whole cell lysates of six independent clones transfected with human GABA_B receptor 1b isoform encoding cDNA. The clones analysed in lanes 4 to 7 express a GABA_B receptor of expected molecular weight (arrow).

25

Figure 3: Expression of human GABA_B receptor 1d isoform in transfected C127 cells.

- 30 Western blot analysis of transfected C127 cells using a polyclonal anti-human GABA_B receptor antibody. Lanes 1-3: Concentrated culture media from three independent C127 clones transfected with a cDNA expression construct encoding the human GABA_B receptor

1d isoform. Lanes 4-6: Whole cell lysates corresponding to the clones analysed in lanes 1-3. The experiment revealed that the human GABA_B receptor 1d cDNA encodes a secreted isoform. The arrow indicates the bands corresponding to the 1d isoform.

5

Figure 4: Expression of human GABA_B receptor 1d isoform in *E. coli*.

Western blot analysis of transformed *E. coli* cells using a polyclonal anti-human GABA_B receptor antibody. Lane 1: Lysate from an uninduced *E. coli* culture transformed with an pET-based expression construct encoding the human GABA_B receptor 1d cDNA. Lane 2: 10 Lysate from an IPTG-induced *E. coli* culture transformed with an expression construct encoding the human GABA_B receptor 1d cDNA. Lane 3: Lysate from an IPTG-induced *E. coli* culture transformed with an expression construct encoding an unrelated protein. Lane 4: The BSA-conjugated peptide previously used for immunization was loaded on the 15 gel as a positive antibody control.

The screening methods according to the invention can e.g. comprise the steps (a) transforming a cultured cell with a nucleic acid molecule encoding a GABA_B receptor, so 20 that a GABA_B receptor is expressed on the surface of the cell; (b) contacting a test compound with the said cell; and (c) determining whether the test compound binds to, and/or activates, the GABA_B receptor.

In particular GABA_B receptor expressing cells, transgenic animals or cells and tissues 25 derived thereof, may be used to screen substance libraries for antagonist or agonist activities. For this purpose, GABA_B receptor expression may be directed to cells and tissues containing, either naturally or artificially, the necessary components allowing correct receptor transport and processing as well as coupling to second messenger pathways. Screening may be performed as ligand binding assays or functional assays. For 30 screening, cells and tissues may be prepared in various ways, each uniquely suited to its purpose. Ligand binding assays are performed *in vivo* or *in vitro* using e.g. radiolabelled GABA. Functional assays exemplified by, but not limited to, Ca⁺⁺-responses, cAMP-

FIGURE 1A

-243	TGACCTCGGGCAGGTCCTGGTGCAGAGCGTCGCCAAAGGACGCCGAGAGGGAGGCGGGGAT	-184
-183	TGCCCAGACATCCTTCAGCGAAGTGCAATGTGTGTTGTAAACCATCGTTGGCTGTCGGGA	-124
-123	GACCGCGAGGACCGGTCCAGGCTGCCGGCGGAGTCGAGGGCGAGGAGAGGCCGCGTGAGT	-64
-63	GAGCAGAGTCCAGAGCCGTGCGCCCCCAGAACTGCGCGCTCCGCCCGGTGCACCCCCCGGC	-4
-3	<u>GCCATG</u> CCCCAGTTGCCCCCGCGGCTCTGCTACGGGCCCGCTCTCCATCATGCGGCCCTCATG	57
58	CCGCTACCAAGGAGGTGGCCAAAGGCAGCATCGGGCGCGGTGTGCTCCCCGCCGTGGAA	117
118	CTGGCCATCGAGCAGATCCGCAACGAGTCACTCCTGCGGCCCTACTTCCCTCGACCTGCGG	177
178	CTCTATGACACGGAGTGCACAAACGAAAGGTTGAAAGCCTTCTACGATGCGATATAAAA	237
238	TACGGGCCGAACCACTTGATGGTGTTTGGAGGCGTCTGTCCATCCGTCACATCCATCATT	297
298	GCAGAGTCCCCTCCAAGGCTGGAATCTGGTGCAGCTTCTTTTGCTGCAACCAACGCTGTT	357
358	CTAGCCGATAAGAAAAAATACCCCTTATTTCTTTCGGACCGTCCCATCAGACAAATGCGGTG	417
418	AATCCAGCCATTCTGAAGTTGCTCAAGCACTACCAGTGGAAAGCGCGTGGGCACGCTGACG	477
478	CAAGACGTTTCAGAGGTTCTCTGAGGTGCGGAATGACCTGACTGGAGTTCTGTATGGCGAG	537

FIGURE 1B

538 GACATTGAGATTTTCAGACACCGAGAGCTTCTCCAACGATCCCTGTACCAGTGTCAAAAAG 597
598 CTGAAGGGGAATGATGTGCGGGATCATCCTTGGCCAGTTTGACCAGAAATATGGCAGCAAAA 657
658 GTGTTCTGTGTGCATACGAGGAGAAACATGTATGTAGTAAATATCAGTGGATCATTCGG 717
718 GGCTGGTACGAGCCTTCTTGGTGGGAGCAGGTGCACACGGAAAGCCAACTCATCCCGCTGC 777
778 CTCGGGAAGAAATCTGCTTGCTGCCATGGAGGGCTACATTGGCGTGGATTTCGAGCCCCCTG 837
838 AGCTCCAAGCAGATCAAGACCATCTCAGGAAAGACTCCACAGCAGTATGAGAGAGAGTAC 897
898 AACAAACAAGCGGTCAGGGCGTGGGGCCCCAGCAAAGTTCCACGGGTACGCCCTACGATGGCATC 957
958 TGGGTCAATCGCCAAGACACTGCAGAGGGCCATGGAGACACTGCATGCCAGCAGCCGGCAC 1017
1018 CAGCGGATCCAGGACTTCAACTACACGGACCACACGCTGGCAGGATCATCCTCAATGCC 1077
1078 ATGAACGAGACCAACTTCTTCGGGGTCACGGGTCAAGTTGTATTCCGGAATGGGAGAGA 1137
1138 ATGGGGACCATTAAATTTACTCAATTTCAAGACAGCAGGGAGGTGAAGGTGGGAGAGTAC 1197
1198 AACGCTGTGGCCGACACACTGGAGATCATCAATGACACCATCAGGTTCCAAAGGATCCGAA 1257
1258 CCACCAAAGACAAGACCATCATCCTGGAGCAGCTGCGGAAGATCTCCTTACCCTCTCTAC 1317

FIGURE 1C

1318	AGCATCCCTCTGTGCCCTCACCATCCTCGGGATGATCATGGCCAGTGCTTTTCTCTTCTTC	1377
1378	AACATCAAGAACCGGAATCAGAAAGCTCATAAAGATGTCGAGTCCATACATGAACAACCTT	1437
1438	ATCATCCTTGGAGGGATGCTTTCCTATGCTTCCATATTCTCTTTGGCCCTTGATGGATCC	1497
1498	TTTGTCTCTGAAAAGACCCTTTGAAACACTTTGCACCGTCAGGACCTGGATTCTCACCCGTG	1557
1558	GGCTACACGACCGCTTTTGGGGCCATGTTTGCAAAAGACCTGGAGAGTCCACGCCATCTTC	1617
1618	AAAAATGTGAAAATGAAGAAGAAGATCATCAAGGACCAGAAACTGCTTGTGATCGTGGGG	1677
1678	GGCATGCTGTGATCGACCTGTGTATCCTGATCTGCTGGCAGGCTGTGGACCCCTGCCGA	1737
1738	AGGACAGTGGAGAAGTACAGCATGGAGCCGGACCCAGCAGGACGGGATATCTCCATCCGC	1797
1798	CCTCTCCCTGGAGCACTGTGAGAACACCCATATGACCATCTGGCTTGGCATCGTCTATGCC	1857
1858	TACAAGGGACTTCTCATGTTGTTCGGTTGTTTCTTAGCTTGGGAGACCCGCAACGTCAGC	1917
1918	ATCCCCGCACTCAACGACAGCAAGTACATCGGGATGAGTGTCTACAACGTGGGGATCATG	1977
1978	TGCATCATCGGGGCCGCTGTCTCCTTCCCTGACCCGGGACCAGCCCAATGTGCAGTTCTGC	2037
2038	ATCGTGGCTCTGGTCATCATCTTCTGCAGCACCATCACCCCTCTGCCCTGGTATTCTGTGCCG	2097

FIGURE 1D

2098	AAGCTCATCACCCCTGAGAAACAAACCCAGATGCAGCAACGCAGAAACAGGCGATTCCAGTTC	2157
2158	ACTCAGAAATCAGAAAGAAAGATTCTAAACGTCACCTCGGTCAACCAGTGTGAACCAA	2217
2218	GCCAGCACATCCCCGCTGGAGGGCCCTACAGTCAGAAACCAATCGCCCTGCCGAATGAAGATC	2277
2278	ACAGAGCTGGATAAAGACTTGGAAGAGGTCACCATGCAGCTGCAGGACACACCAGAAAG	2337
2338	ACCACCTACATTAAACAGAACCACTACCAAGAGCTCAATGACATCCTCAACCTGGGAAC	2397
2398	TTCACTGAGAGCACAGATGGAGGAAAGGCCATTTTAAAAAATCACCTCGATCAAAATCCC	2457
2458	CAGCTACAGTGGAAACAAACAGAGCCCTCTCGAACATGCAAAAGATCCTATAGAAGATATA	2517
2518	AACTCTCCAGAACACATCCAGCGTCGGCTGTCCCTCCAGCTCCCCCATCTCCACCACGCC	2577
2578	TACCTCCCATCCATCGGAGGCGTGGACGCCAGCTGTGTCAGCCCTCGGTCAGCCCCACC	2637
2638	GCCAGCCCCGCCACAGACATGTGCCACCCCTCCTTCCGAGTCATGGTCTCGGGCCTGTAA	2697
2698	GGGTGGAGGCCCTGGGCCCGGGGCCCTCCCCCGTGACAGAAACCACTGGGCAGAGGGGTC	2757
2758	TGCTGCAGAAACACTGTGCGCTCTGGCTGCGGAGAAAGCTGGGCACCATGGCTGGCCTCTC	2817
2818	AGGACCACTCGGATGGCCTCAGGTGGACAGGACGGGGCAGGGGAGAGACTTGGCACCTGA	2877

FIGURE 1E

2878	CCTCGAGCCTTATTGTGAAGTCCTTATTCTTCACAAAGAGGAAACGGAAATGGGAC	2937
2938	GTCTTCCCTTAACATCTGCAAAACAAGGAGCGCTGGGATATCAAACTTGCAAAAAA	2997
2998	AAAA	3001

FIGURE 2A

1	M	P	S	C	P	A	R	S	A	T	G	P	L	S	I	M	G	L	M	P	20
21	L	T	K	E	V	A	K	G	S	I	G	R	G	V	L	P	A	V	E	L	40
41	A	I	E	Q	I	R	N	E	S	L	L	R	P	Y	F	L	D	L	R	L	60
61	Y	D	T	E	C	D	N	A	K	G	L	K	A	F	Y	D	A	I	K	Y	80
81	G	P	N	H	L	M	V	F	G	G	V	C	P	S	V	T	S	I	I	A	100
101	E	S	L	Q	G	W	N	L	V	Q	L	S	F	A	A	T	T	P	V	L	120
121	A	D	K	K	K	Y	P	Y	F	F	R	T	V	P	S	D	N	A	V	N	140
141	P	A	I	L	K	L	L	K	H	Y	Q	W	K	R	V	G	T	L	T	Q	160
161	D	V	Q	R	F	S	E	V	R	N	D	L	T	G	V	L	Y	G	E	D	180
181	I	E	I	S	D	T	E	S	F	S	N	D	P	C	T	S	V	K	K	L	200
201	K	G	N	D	V	R	I	I	L	G	Q	F	D	Q	N	M	A	A	K	V	220
221	F	C	C	A	Y	E	E	N	M	Y	G	S	K	Y	Q	W	I	I	P	G	240

FIGURE 2B

241	W	Y	E	P	S	W	W	E	Q	V	H	T	E	A	N	S	S	R	C	L	260
261	R	K	N	L	L	A	A	M	E	G	Y	I	G	V	D	F	E	P	L	S	280
281	S	K	Q	I	K	T	I	S	G	K	T	P	Q	Q	Y	E	R	E	Y	N	300
301	N	K	R	S	G	V	G	P	S	K	F	H	G	Y	A	Y	D	G	I	W	320
321	V	I	A	K	T	L	Q	R	A	M	E	T	L	H	A	S	S	R	H	Q	340
341	R	I	Q	D	F	N	Y	T	D	H	T	L	G	R	I	I	L	N	A	M	360
361	N	E	T	N	F	F	G	V	T	G	Q	V	V	F	R	N	G	E	R	M	380
381	G	T	I	K	F	T	Q	F	Q	D	S	R	E	V	K	V	G	E	Y	N	400
401	A	V	A	D	T	L	E	I	I	N	D	T	I	R	F	Q	G	S	E	P	420
421	P	K	D	K	T	I	I	L	E	Q	L	R	K	I	S	L	P	L	Y	S	440
441	I	L	S	A	L	T	I	L	G	M	I	M	A	S	A	F	L	F	N		460
461	I	K	N	R	N	Q	K	L	I	K	M	S	S	P	Y	M	N	L	I		480

FIGURE 2C

481	I	L	G	G	M	L	S	Y	A	S	I	F	L	F	G	L	D	G	S	F	500
501	V	S	E	K	T	F	E	T	L	C	T	V	R	T	G	I	L	T	V	G	520
521	Y	T	A	M	F	G	A	M	F	A	K	T	W	R	K	H	A	I	F	K	540
541	N	V	K	M	K	K	K	I	I	K	D	Q	K	L	V	I	V	G	G	560	
561	M	L	L	I	D	L	C	I	L	I	C	W	Q	A	V	D	P	L	R	580	
581	T	V	E	K	Y	S	M	E	P	D	P	A	G	R	D	I	S	I	R	P	600
601	L	L	E	H	C	E	N	T	H	M	T	I	W	L	G	I	V	Y	A	Y	620
621	K	G	L	L	M	L	F	G	C	F	L	A	W	E	T	R	N	V	S	I	640
641	P	A	L	N	D	S	K	Y	I	G	M	S	V	Y	N	V	G	I	M	C	660
661	I	I	G	A	A	V	S	F	L	T	R	D	Q	P	N	V	Q	F	C	I	680
681	V	A	L	V	I	I	F	C	S	T	I	T	L	C	L	V	F	V	P	K	700
701	L	I	T	L	R	T	N	P	D	A	A	T	Q	N	R	R	F	Q	F	T	720

FIGURE 2D

9/51

721	Q	N	Q	K	K	E	D	S	K	T	S	T	S	V	T	S	V	N	Q	A	740
741	S	T	S	R	L	E	G	L	Q	S	E	N	H	R	L	R	M	K	I	T	760
761	E	L	D	K	D	L	E	E	V	T	M	Q	L	Q	D	T	P	E	K	T	780
781	T	Y	I	K	Q	N	H	Y	Q	E	L	N	D	I	L	N	L	G	N	F	800
801	T	E	S	T	D	G	G	K	A	I	L	K	N	H	L	D	Q	N	P	Q	820
821	L	Q	W	N	T	T	E	P	S	R	T	C	K	D	P	I	E	D	I	N	840
841	S	P	E	H	I	Q	R	R	L	S	L	Q	L	P	I	L	H	A	Y		860
861	L	P	S	I	G	G	V	D	A	S	C	V	S	P	C	V	S	P	T	A	880
881	S	P	R	H	R	H	V	P	P	S	F	R	V	M	V	S	G	L			898

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1	ATGGCTTCCCCCGGAGCTCCGGGCAGCCCCGGGCCCGCGCGCGCGCGCGCGC	60
61	CGCCTGCTGTGCCCCTGCTGTGCTGCTGCTGTGTTGGCGCCCGGGCCTGGGC	120
121	TGGACGGGGGCGCCCCCGGCCCGCCAGCAGCCCCCGCTCTCCATCATGGGCCTC	180
181	ATGCCGCTCACCAAGGAGGTGGCCAAGGCAGCATCGGGCGGCGTGCTCCCCGCCGTG	240
241	GAGCTAGCCATCGAGCAGATCCGCAACGAGTCACTCCTGCGCCCCCTACTTCCTGGACCCTG	300
301	CGACTCTATGACACCGAGTGTGACAATGCAAAGGGACTGAAGCCTTCTATGACGCAATA	360
361	AAGTATGGGGCCGAACCATTTGATGTTGTTGGAGGCGTCTGTCCGTCTGTCACATCTATT	420
421	ATCGCGGAGTCCCTCCAAGGCTGGAATCTGGTGCAGCTTTCCTTCGCCGCCACCACGCCT	480
481	GTTCTTTCGGATAAGAAGAAGTACCCGTATTTCCTCCGGACGGTGCCGTGAGACAACGCG	540
541	GTGAACCCCGCCATCCTGAAGCTCCTGAAGCACTTCGCTGGCGCGTGTGGCACAACCTC	600
601	ACGCAGGACGTGCAGCGCTTCTCCGAGGTGAGGAATGACCTGACTGGGGTTCTGTATGGG	660
661	GAAGATATTGAGATCTCAGACACAGAGAGTTTCTCCAATGATCCCCTGCAACCAGCGTCAAA	720
721	AAGCTCAAGGGGAATGACGTGCGGATCATCCTTGGCCAGTTTGACCAGAAATATGGCAGCA	780
781	AAAGTCTTCTGTGTGCCCTTCGAGGAGAGCATGTTTTGGCAGCAAGTACCAGTGGATCATC	840

FIGURE 3B

841 CCGGGATGGTACGAGCCCTGCGTGGTGGGAGCAGGTGCATGTGGAGGCCAATTCCCTCACGC 900
901 TGCCTGCGCAGAAAGCCCTCCCTGGCTGCCATGGAAGGTTACATCGGAGTGGACTTTGAGCCC 960
961 CTGAGCTCCAAACAAATCAAGACCATCTCAGGGAAGACTCCACAGCAGTATGAAAAGAGAG 1020
1021 TACAACAGCAAAACGTTTCAGGCGTGGGGCCCCAGCAAGTTCCATGGGTACGCCCTACGATGGG 1080
1081 ATCTGGGTCAATCGCCCAAGACCCCTACAGAGGGCCCATGGAGACACTGCATGCCAGTAGCAGG 1140
1141 CACCAGCGGATCCAGGACTTCAACTACACAGACCACACGCTGGGCAAAATCATCCTCAAT 1200
1201 GCCATGAACGAGACCAACTTCTTCGGGGTCAACGGGTCAAGTTGTGTTCCGGAACGGGGAG 1260
1261 AGAATGGGAACCATTAATTTACTCAATTTCAAGACAGCAGAGAGGTGAAGTCTGGCGAA 1320
1321 TACAACGCGGTGGCTGACACACTGGAGATCATCAATGACACCATAAGGTTCCAGGGGTCC 1380
1381 GAGCCACCCAAAGACAAGACCATCATTTCTGGAGCAGCTTCGGAAGATCTCGCTTCCACTG 1440
1441 TATAGCATCCTGTCCGCTCTCACCATCCTCGGCATGATCATGGCCAGCGCCTTCCCTCTTC 1500
1501 TTCAACATCAAGAACCGGAACCAAAAGCTGATTAAGATGTCAAGCCCCCTACATGAACAAC 1560
1561 CTCATCATCCTGGGAGGAATGCTGTCCCTATGCATCCATCTTCCCTCTTTGGCCCTCGATGGG 1620
1621 TCCTTCGTCTCAGAAAAAGACCCTTTGAAAACACTCTGCACGGTCCGGACCTGGATTCTCACC 1680

FIGURE 3C

1681	GTGGGCTACACAACTGCCCTTTGGGGCCATGTTTGCAAAGACCTGGAGGGTCCATGCCATC	1740
1741	TTCAAAAATGTGAAGATGAAGAAGATCATCAAAGACCAGAAAGCTGCTTGTGATTTGTG	1800
1801	GGGGCATGCTGCTCATCGACCTGTGCATCCTGATCTGTTGGCAGGCTGTGGACCCCTTG	1860
1861	CGGAGGACAGTAGAGAGGTACAGCATGGAGCCGGACCCAGCAGGCCGGGACATCTCCATC	1920
1921	CGCCCATTTGCTGGAAACACTGCCGAAAAACACCCACATGACCATCTGGCTTGGCATTTGTCTAC	1980
1981	GCCTACAAAGGGGCTCCTCATGCTATTTCGGTTGTTTCTTGGCATGGGAAAAACCGCAATGTG	2040
2041	AGCATCCCCTGCCCTCAACGACAGCAAAGTACATCGGCATGAGTGTGTACAAATGTGGGGATC	2100
2101	ATGTGCATCATCGGGGCTGCTGTCTCCTTCCCTGACGCGTGAACAGCCCAACGTGCAGTTC	2160
2161	TGCATCGTGGCCCTGGTCAATCATCTTCTGCAGCACCATCACTCTCTGCCCTGGTGTGTG	2220
2221	CCAAAGCTCATTTACTCTGAGGACAAACCCCTGACGCAGCCACTCAGAACAGGCGGTCCAG	2280
2281	TTCACACAGAAACCAGAAAGAAAGATTTCGAAGACCTCCACTTCAGTCAACAGCGTGAAC	2340
2341	CAGCGGAGCACGTACGGCCTGGAGGGACTGCAGTCAAGAAAACCCGCCCTTCGAATGAAG	2400
2401	ATCACAGAGCTGGACAAAAGACTTTGGAAGAAGTCAACCATGCAGCTACAAGACACACAGAG	2460
2461	AAGACCACATACATCAAACAGAAATCACTACCAAGAGCTCAACGACATCCTCAGCTTGGGC	2520

FIGURE 3D

2521	AACTTCACAGAGACAGATGGAGGAAAGGCCATTCTAAAAAATCACCTCGATCAAAAC	2580
2581	CCCCAGCTCCAGTGGAACACGACAGAGCCCCTCAAGAACATGCAAAAGACCCCATAGAAGAC	2640
2641	ATCAACTCCCCGGAGCACATCCAGCGCCGGCTGTGCTCCAGCTCCCCCATCCTTCACCAC	2700
2701	GCCTACCTCCCATCCATCGGAGGCGTGGATGCCAGCTGCGTCAGCCCCCTGTGTACGCCCT	2760
2761	ACCGCCAGCCCCTCGCCACAGACACGTACCAACCCTCCTTCCGAGTCAATGGTCTCGGGCCTG	2820
2821	<u>TAG</u>	2823

FIGURE 4A

1	M	A	S	P	P	S	S	G	Q	P	R	P	P	P	P	P	P	P	A	20
21	R	L	L	L	P	L	L	L	S	L	L	L	W	L	A	P	G	A	W	40
41	W	T	R	G	A	P	R	P	P	P	S	S	P	P	L	S	I	M	G	60
61	M	P	L	T	K	E	V	A	K	G	S	I	G	R	G	V	L	P	A	80
81	E	L	A	I	E	Q	I	R	N	E	S	L	L	R	P	Y	F	L	D	100
101	R	L	Y	D	T	E	C	D	N	A	K	G	L	K	A	F	Y	D	A	120
121	K	Y	G	P	N	H	L	M	V	F	G	G	V	C	P	S	V	T	S	140
141	I	A	E	S	L	Q	G	W	N	L	V	Q	L	S	F	A	A	T	T	160
161	V	L	A	D	K	K	K	Y	P	Y	F	F	R	T	V	P	S	D	N	180
181	V	N	P	A	I	L	K	L	L	K	H	F	R	W	R	R	V	G	T	200
201	T	Q	D	V	Q	R	F	S	E	V	R	N	D	L	T	G	V	L	Y	220
221	E	D	I	E	I	S	D	T	E	S	F	S	N	D	P	C	T	S	V	240
241	K	L	K	G	N	D	V	R	I	I	L	G	Q	F	D	Q	N	M	A	260

FIGURE 4B

261	K	V	F	C	C	A	F	E	E	S	M	F	G	S	K	Y	Q	W	I	I	280
281	P	G	W	Y	E	P	A	W	E	Q	V	H	V	E	A	N	S	S	R	300	
301	C	L	R	R	S	L	L	A	A	M	E	G	Y	I	G	V	D	F	E	P	320
321	L	S	S	K	Q	I	K	T	I	S	G	K	T	P	Q	Q	Y	E	R	E	340
341	Y	N	S	K	R	S	G	V	G	P	S	K	F	H	G	Y	A	Y	D	G	360
361	I	W	V	I	A	K	T	L	Q	R	A	M	E	T	L	H	A	S	S	R	380
381	H	Q	R	I	Q	D	F	N	Y	T	D	H	T	L	G	K	I	I	L	N	400
401	A	M	N	E	T	N	F	F	G	V	T	G	Q	V	V	F	R	N	G	E	420
421	R	M	G	T	I	K	F	T	Q	F	Q	D	S	R	E	V	K	V	G	E	440
441	Y	N	A	V	A	D	T	L	E	I	I	N	D	T	I	R	F	Q	G	S	460
461	E	P	P	K	D	K	T	I	I	L	E	Q	L	R	K	I	S	L	P	L	480
481	Y	S	I	L	S	A	L	T	I	L	G	M	I	M	A	S	A	F	L	F	500
501	F	N	I	K	N	R	N	Q	K	L	I	K	M	S	S	P	Y	M	N	N	520
521	L	I	I	L	G	M	L	S	Y	A	S	I	F	L	F	G	L	D	G	540	

FIGURE 4C

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541	S	F	V	S	E	K	T	F	E	T	L	C	T	V	R	T	W	I	L	T	560
561	V	G	Y	T	A	F	G	A	M	F	A	K	T	W	R	V	H	A	I	580	
581	F	K	N	V	K	M	K	K	I	I	K	D	Q	K	L	L	V	I	V	600	
601	G	G	M	L	L	I	D	L	C	I	L	I	C	W	Q	A	V	D	P	L	620
621	R	R	T	V	E	R	Y	S	M	E	P	D	P	A	G	R	D	I	S	I	640
641	R	P	L	L	E	H	C	E	N	T	H	M	T	I	W	L	G	I	V	Y	660
661	A	Y	K	G	L	L	M	L	F	G	C	F	L	A	W	E	T	R	N	V	680
681	S	I	P	A	L	N	D	S	K	Y	I	G	M	S	V	Y	N	V	G	I	700
701	M	C	I	I	G	A	A	V	S	F	L	T	R	D	Q	P	N	V	Q	F	720
721	C	I	V	A	L	V	I	I	F	C	S	T	I	T	L	C	L	V	F	V	740
741	P	K	L	I	T	L	R	T	N	P	D	A	A	T	Q	N	R	R	F	Q	760
761	F	T	Q	N	Q	K	K	E	D	S	K	T	S	T	S	V	T	S	V	N	780
781	Q	A	S	T	S	R	L	E	G	L	Q	S	E	N	H	R	L	R	M	K	800
801	I	T	E	L	D	K	D	L	E	E	V	T	M	Q	L	Q	D	T	P	E	820

FIGURE 4D

821	K	T	T	Y	I	K	Q	N	H	Y	Q	E	L	N	D	I	L	S	L	G	840
841	N	F	T	E	S	T	D	G	G	K	A	I	L	K	N	H	L	D	Q	N	860
861	P	Q	L	Q	W	N	T	T	E	P	S	R	T	C	K	D	P	I	E	D	880
881	I	N	S	P	E	H	I	Q	R	R	L	S	L	Q	L	P	I	L	H	H	900
901	A	Y	L	P	S	I	G	G	V	D	A	S	C	V	S	P	C	V	S	P	920
921	T	A	S	P	R	H	R	H	V	P	P	S	F	R	V	M	V	S	G	L	940

FIGURE 5A

1	M	P	S	C	P	A	R	S	A	T	G	P	L	S	I	M	G	L	M	P	20
21	L	T	K	E	V	S	K	G	S	I	G	R	G	V	L	P	A	V	E	L	40
41	A	I	E	Q	I	S	N	E	S	L	L	R	P	Y	F	L	D	L	R	L	60
61	Y	D	T	E	C	K	N	A	K	G	L	K	A	F	Y	D	A	I	K	Y	80
81	G	P	N	H	L	G	V	F	G	G	V	C	P	S	V	T	S	I	I	A	100
101	E	S	L	Q	G	V	N	L	V	Q	L	S	F	A	A	T	T	P	V	L	120
121	A	D	K	K	K	F	P	Y	F	F	R	T	V	P	S	D	N	A	V	N	140
141	P	A	I	L	K	H	L	K	H	Y	Q	W	K	R	V	G	T	L	T	Q	160
161	D	V	Q	R	F	R	E	V	R	N	D	L	T	G	V	L	Y	G	E	D	180
181	I	E	I	S	D	F	E	S	F	S	N	D	P	C	T	S	V	K	K	L	200
201	K	G	N	D	V	L	I	I	L	G	Q	F	D	Q	N	M	A	A	K	V	220
221	F	C	C	A	Y	M	E	N	M	Y	G	S	K	Y	Q	W	I	I	P	G	240
241	W	Y	E	P	S	Q	W	E	Q	V	H	T	E	A	N	S	S	R	C	L	260
261	R	K	N	L	L	E	A	M	E	G	Y	I	G	V	D	F	E	P	L	S	280
281	S	K	Q	I	K	G	I	S	G	K	T	P	Q	Q	Y	E	R	E	Y	N	300
301	N	K	R	S	G	S	G	P	S	K	F	H	G	Y	A	Y	D	G	I	W	320

FIGURE 5B

321	V	I	A	K	T	L	Q	R	A	M	E	T	L	H	A	S	S	R	H	Q	340
341	R	I	Q	D	F	N	Y	T	D	H	T	L	G	R	I	I	L	N	A	M	360
361	N	E	T	N	F	F	G	V	T	G	Q	V	V	F	R	N	G	E	R	M	380
381	G	T	I	K	F	T	Q	F	Q	D	S	R	E	V	K	V	G	E	Y	N	400
401	A	V	A	D	T	L	E	I	I	N	D	T	I	R	F	Q	G	S	E	P	420
421	P	K	D	K	T	I	I	L	E	Q	L	R	K	I	S	L	P	L	Y	S	440
441	I	L	S	A	L	T	I	L	G	M	I	M	A	S	A	F	L	F	F	N	460
461	I	K	N	R	N	Q	K	L	I	K	M	S	S	P	Y	M	N	N	L	I	480
481	I	L	G	G	M	L	S	Y	A	S	I	F	L	F	G	L	D	G	S	F	500

FIGURE 5C

501	V	S	E	K	T	F	E	T	L	C	T	V	R	T	W	I	L	T	V	G	520
521	Y	T	A	F	G	A	M	F	A	K	T	W	R	V	H	A	I	F	K	540	
541	N	V	K	M	K	K	I	I	K	D	Q	K	L	L	V	I	V	G	G	560	
561	M	L	I	D	L	C	I	L	I	C	W	Q	A	V	D	P	L	R	R	580	
581	T	V	E	K	Y	S	M	E	P	D	P	A	G	R	D	I	S	I	R	P	600
601	L	L	E	H	C	E	N	T	H	M	T	I	W	L	G	I	V	Y	A	Y	620
621	K	G	L	L	M	L	F	G	C	F	L	A	W	E	T	R	N	V	S	I	640

FIGURE 5D

641	P	A	L	N	D	S	K	Y	I	G	M	S	V	Y	N	V	G	I	M	C	660
661	I	I	G	A	A	V	S	F	L	T	R	D	Q	P	N	V	Q	F	C	I	680
681	V	A	L	V	I	I	F	C	S	T	I	T	L	C	L	V	F	V	P	K	700
701	L	I	T	L	R	T	N	P	D	A	A	T	Q	N	R	R	F	Q	F	T	720
721	Q	N	Q	K	K	E	D	S	K	T	S	T	S	H	V	T	S	V	N	A	740
741	S	T	S	R	L	E	G	L	Q	S	E	N	H	R	M	L	R	M	K	I	760
761	E	L	D	K	D	L	E	E	V	T	M	Q	L	Q	P	T	T	P	E	K	780
781	T	Y	I	K	Q	N	H	Y	Q	E	L	N	D	I	L	N	D	L	G	N	800
801	T	E	S	T	D	G	G	K	A	I	L	K	H	D	L	L	D	Q	N	P	820
821	L	Q	W	N	T	T	E	P	S	R	T	C	D	P	I	I	E	H	D	I	840
841	S	P	E	H	I	Q	R	L	S	S	L	Q	P	P	I	L	H	A	Y	A	860
861	L	P	S	I	G	G	V	D	A	S	C	V	S	P	C	V	S	P	T	A	880
881	S	P	R	H	R	H	V	P	P	S	F	R	V	M	V	S	G	L			898

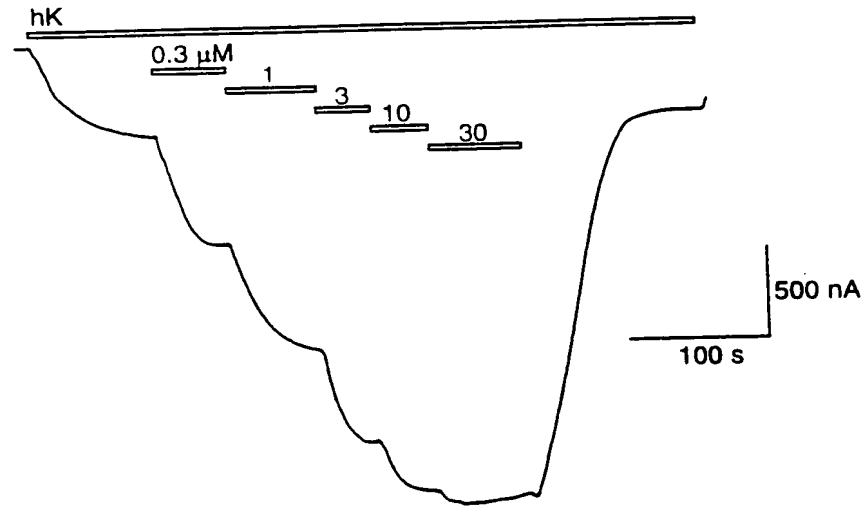
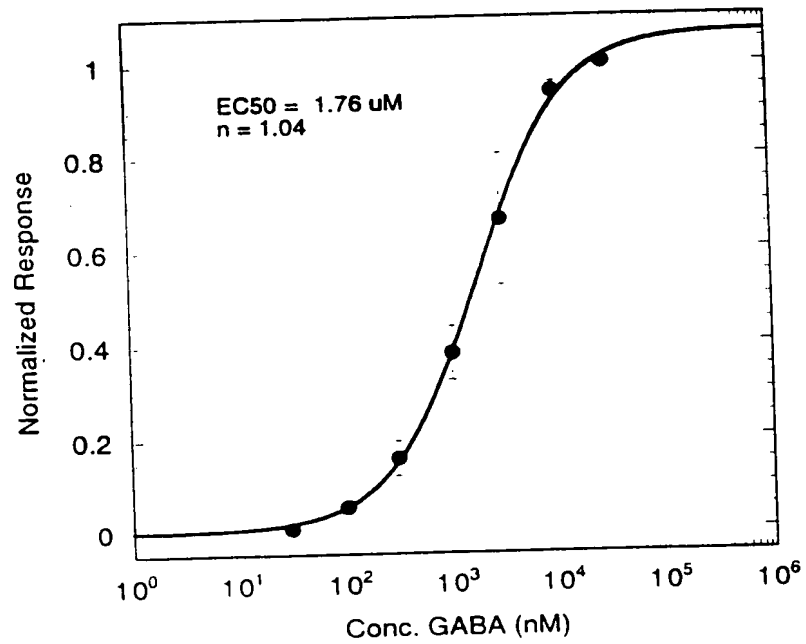
Figure 6A**Figure 6B**

Figure 7

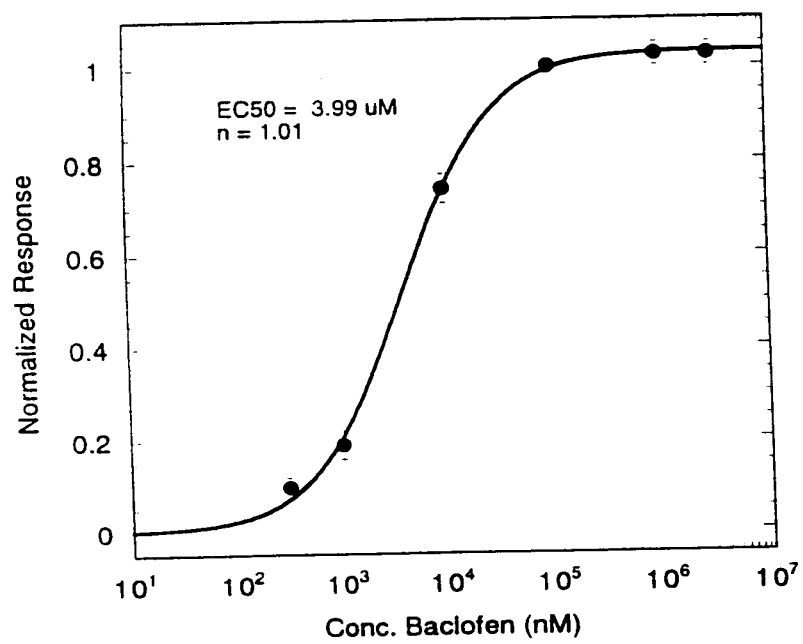


Figure 8

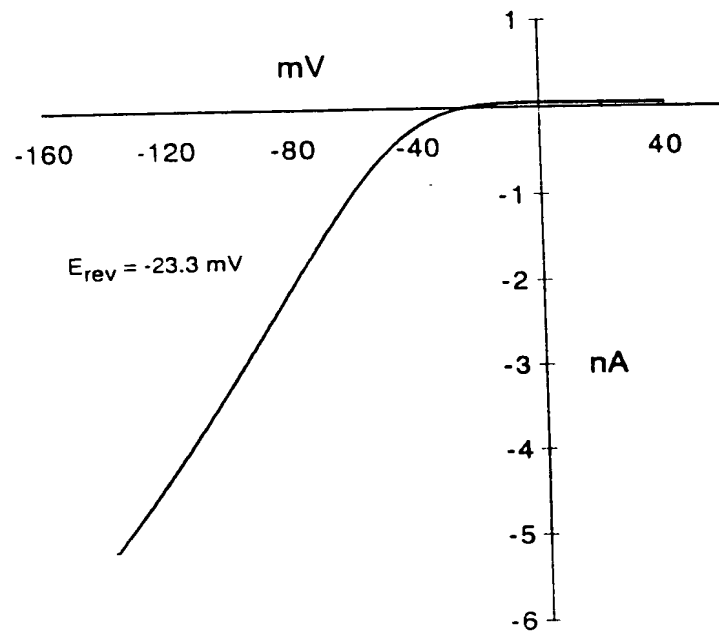


Figure 9A

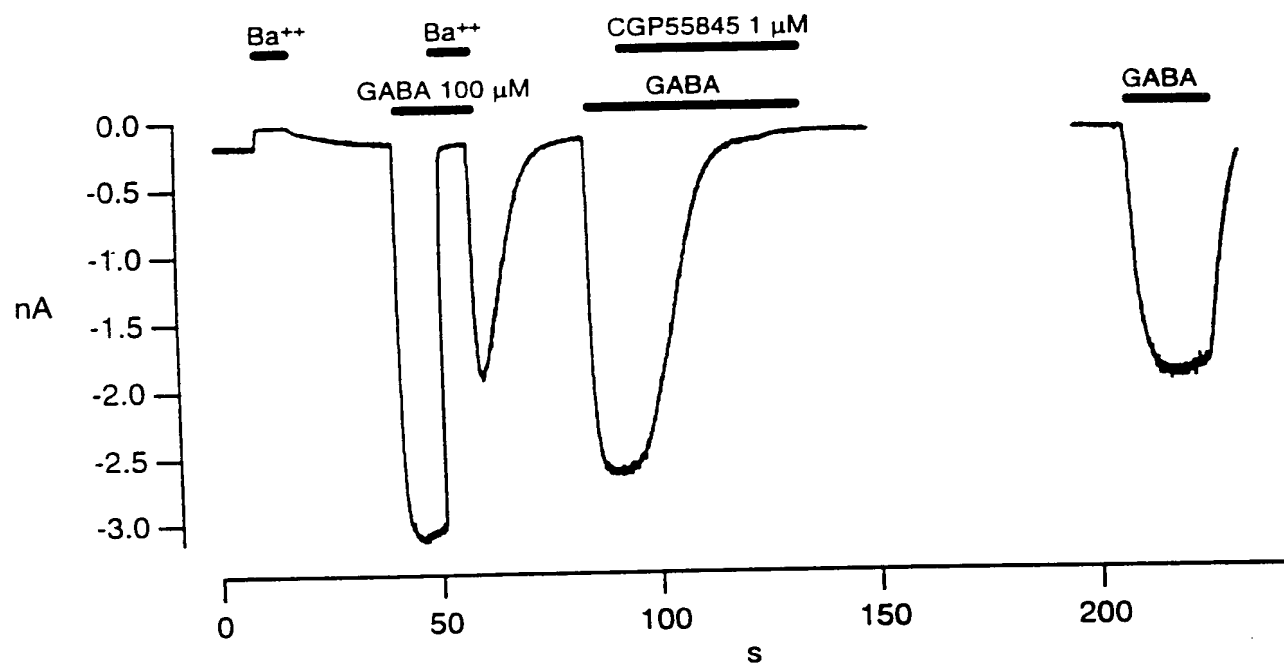
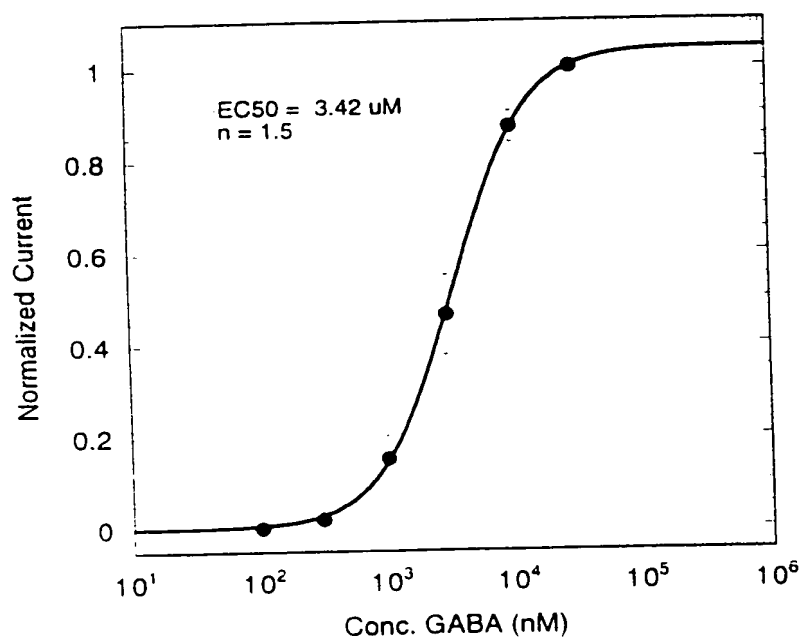


Figure 9B



Figur 10

rGABA ₈ R2	MASPPSSGQPRPPPPPPARLLPLLLSLLWLAPGAWGWRGAPRPPSPSP...LSIMGLMPLTK	65
rGABA ₈ R1bMGPGGCTPVGWPLPLLLVMAAGVAPWASHPLPRPHPRVPPHPSSERRAVYIGALFP	60
rGABA ₈ R2	EVAKGSIGRGVLPAVELAIEQIRN.ESLLRPYFLDLRLDYTECDNAKGLKAFYDAIKYGNHLMVFGGVC	134
rGABA ₈ R1b	MSGWPGGQACQPAVEMALEDVNSRRDILPDYELKLIHHDSCDPCGQATKYLYELLYNDPIKILMPG.C	129
rGABA ₈ R2	PSVTISIIAESLQGNLVQLSFAATTPVLADKKKYPYFFRTVPSDNAVNPAILKLLKHFRWRRVGTLTQDV	204
rGABA ₈ R1b	SSVSTLVAEAAARMWNLI VLSYGSSSPALSNRQRFPTFFRTHPSATLHNPTRVKLFKKGWKKIATIQTT	199
rGABA ₈ R2	QRFSEVRNDLTGVLYGEDIESTESFSNDPCTSVKKLKGNDVRIILQGFQDNMAAKVFCCAFESMFSG	274
rGABA ₈ R1b	EVFTSTLDDLEERVKEAGIEITFRQSFFSDPAVPVKNLKRQDARIIVGLFYETEARKVFCVYKERLFGK	269
rGABA ₈ R2	KYQWIIIPGWYEPAWWEQVHVEANSRCLRRSLLAAMEGYIGVDFEPLSSKQIKTISGKTPQQYEREYNSK	344
rGABA ₈ R1b	KYVWFLIGWYADNWFKTYDPSIN...CTVEEMTEAVEGHIITTEIVMLNPANTRISINMTSQEFV.EKLT	335
rGABA ₈ R2	RSGVGPSKFHY.....AYDGIWVIAKTLQRAMETLHIASSKHQRIQDFNYTDHTLTKIILNAMNETNFFG	409
rGABA ₈ R1b	RLKRHPETGGFQEAPLAYDAI WALALALNKTSGGGRSG..VRLEDFNYYNQTTITDQIYRAMNSSSFEG	403
rGABA ₈ R2	VTGQVVF.RNGERMGTIKFTQFQDSREVKVGEYNAVADTLEIINDTIRFQGSPPPKDKTIILEQLRKISL	478
rGABA ₈ R1b	VSGHVVFASGRMAWTLIEQLQGGSYKKIGYYDSTKDDLS.WSKTDKWIIGGSPPADQTLVIKTRFRFLSQ	472
rGABA ₈ R2	PLYSILSALTILGMIMASAFLEFNKRNQKLKIMSSPYMNNLIILGMLSYASIFLFGLDGSFVSEKTF	548
rGABA ₈ R1b	KLFISVSVLSLIGIVLAVVCLSFNIYNSHVRYIQNSQPNLNNLTAVGCSLALAAVPLGLDGYHIGRSQF	542
rGABA ₈ R2	ETLCTVTRTWILTGVYTTAFGAMFAKTWRVHAIFKNVKKKK...KIIDQKLLVIVGGMLLIDLICILCWQ	615
rGABA ₈ R1b	PFVCQARLWLLGLGSLGYGSMFTKIWWVHTVFTKKEKKWKRTLEPWKLYATVGLLVGMDVLTIAIWQ	612
rGABA ₈ R2	AVDPLRRTVERYSMEDPAGRDISIRPLLEHCENTHMTIWLGIYVAYKGLLMLFGCFLAWETRNVSIPAL	685
rGABA ₈ R1b	IVDPLHRTIETFAKEEPKEDIIVSILPQLEHCSSKKMNTWLGIIFYGYKGLLLLLGIFLAYETKSVSTEKI	682
rGABA ₈ R2	NDSKYIGMSVYVNGIMCIIIGAAVSFLTRDQPNVQFCIVALVIFCSTITLCLVFPVKLITLRTNPDAATQ	755
rGABA ₈ R1b	NDHRAVGMAIYNVAVLCLITAPVTMILSSQDAFAFASLAIVFSSYITLWLVFPKMRRLITRGE....	748
rGABA ₈ R2	NRRFQFTQNKKEDSKTSTSVTSVNQASTSRLEGLOSENHRLRMKITELDKDLEEVMTQLQDTPEKTTYI	825
rGABA ₈ R1bWQSETQDTMKTGSS.TNNNEEEKSRL..LEKENRELEKIIAEKEERSVSELRHQLQSRQQLRSR	809
rGABA ₈ R2	KQNHQELNDILSLGNFTESTDGGKAILKNHLDQNPQLQWNTTEPSRTCKDPIEDINSPEHIQRRLSQL	895
rGABA ₈ R1b	HPPTPPDPSGGLPRGPSEPPDLSCDGSRVHLLYK*.....	845
rGABA ₈ R2	PILHHAYLPISIGGVDA SCVSPCVSPTASPRHRHVPPSFRVMVSGL*.....	940

Figure 11A



Figure 11B



Figure 11C



Figure 11D



Figure 12A



Figure 12B



Figure 13A

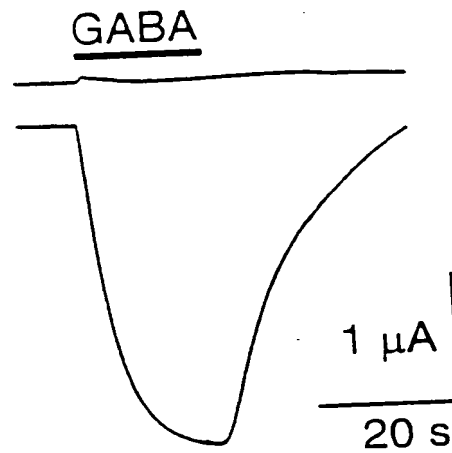


Figure 13B

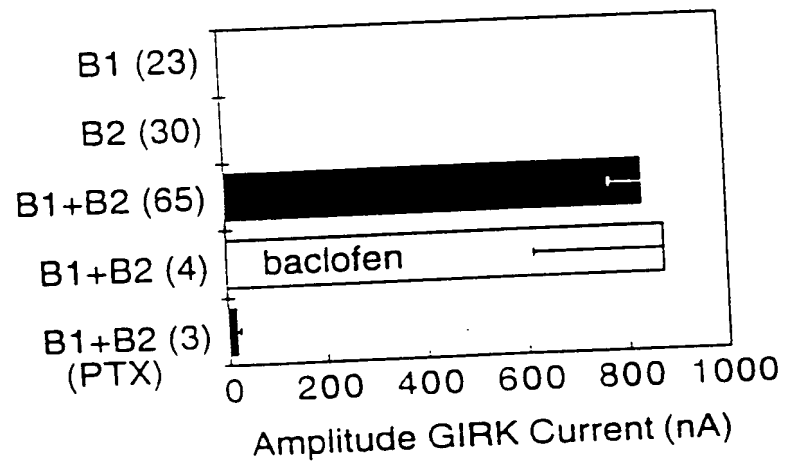


Figure 14A

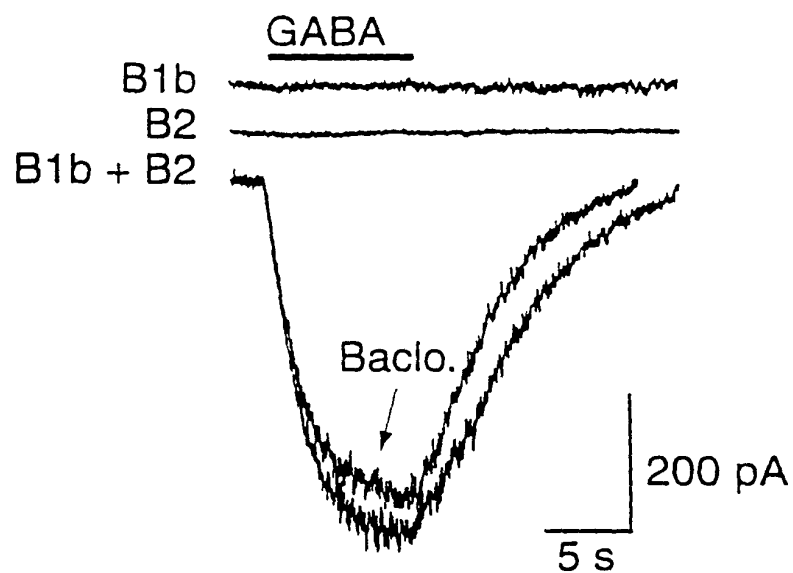


Figure 14B

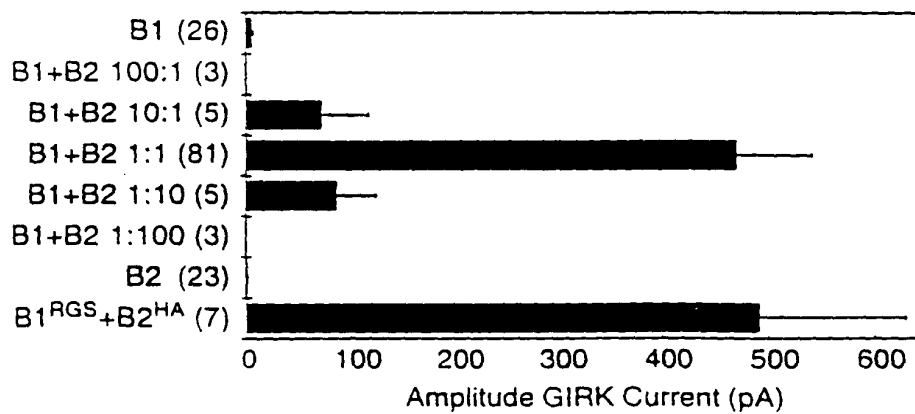


Figure 15A

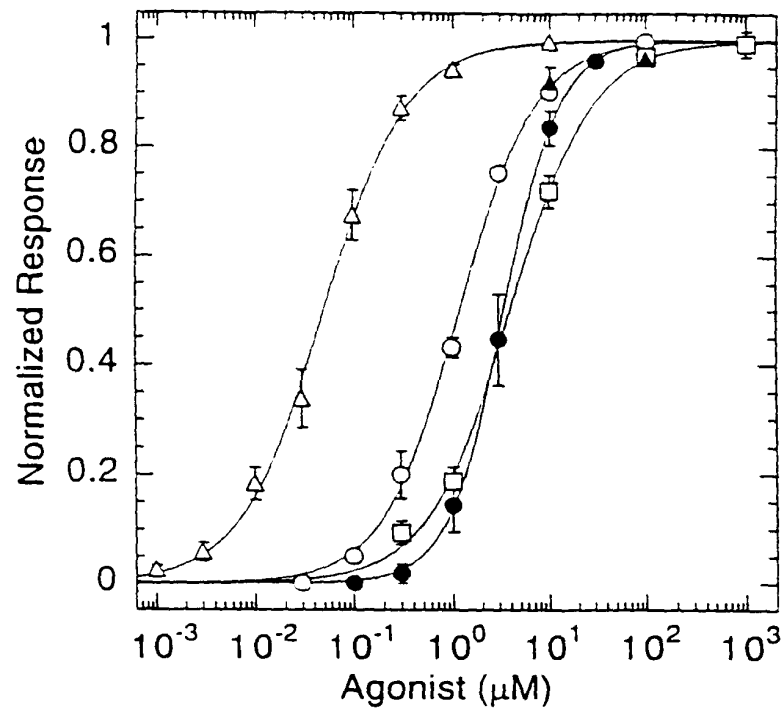


Figure 15B

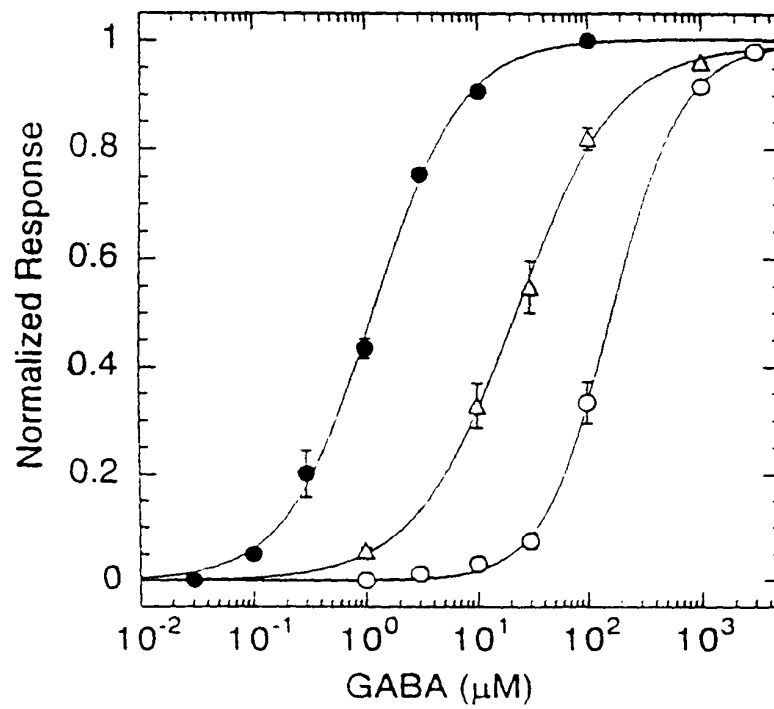


Figure 16

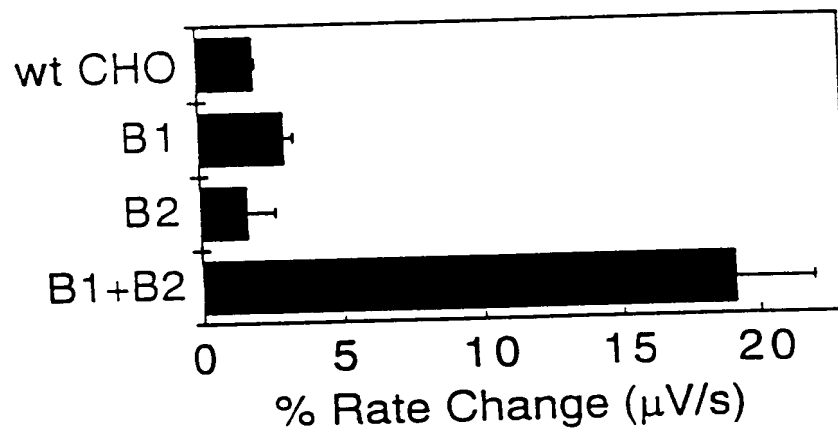


Figure 17A



Figure 17B



Figure 17C



Figure 17D



Figure 18A



Figure 18B

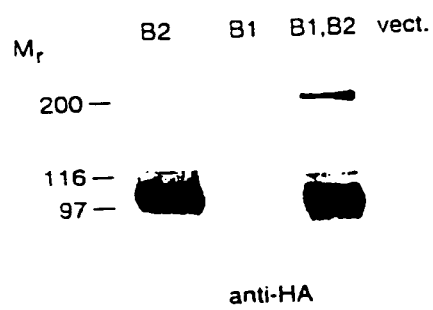
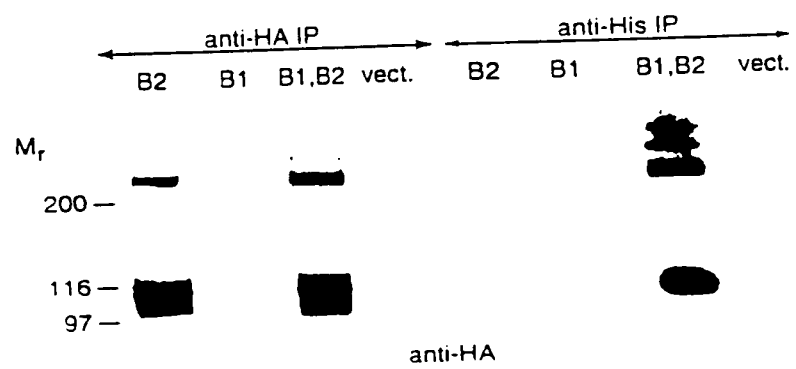


Figure 18C



Silver grain density:

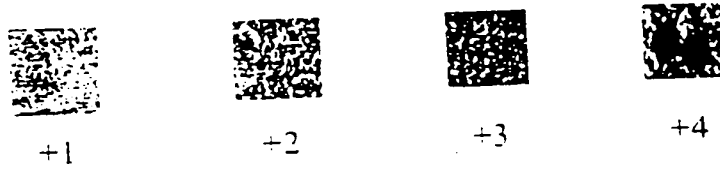


FIGURE 19A



FIGURE 19B

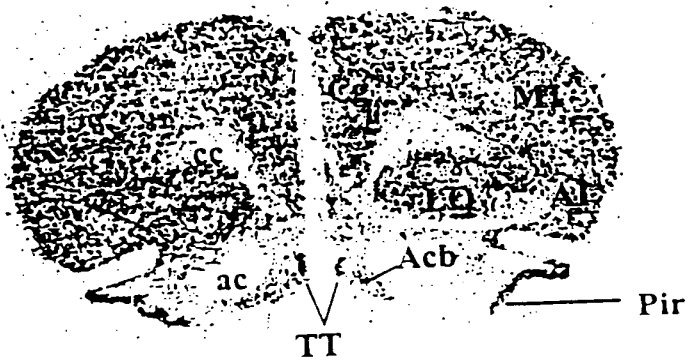


FIGURE 19C

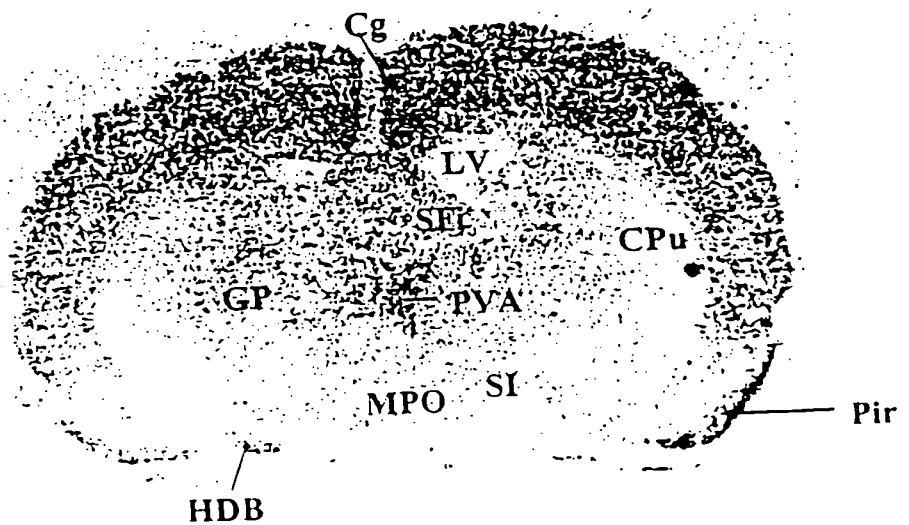


FIGURE 19D

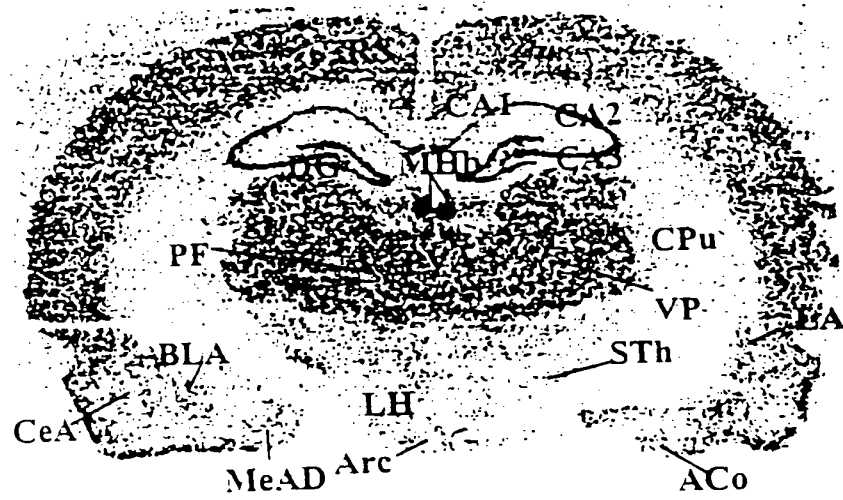


FIGURE 19E

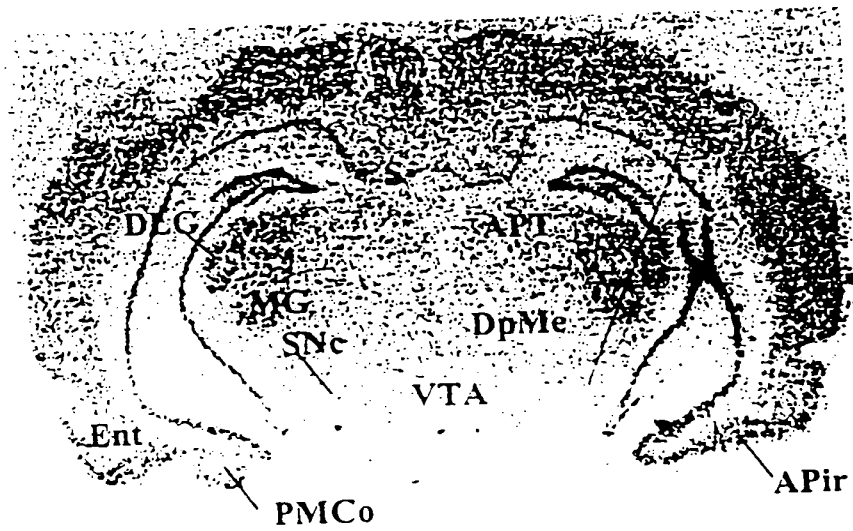


FIGURE 19F

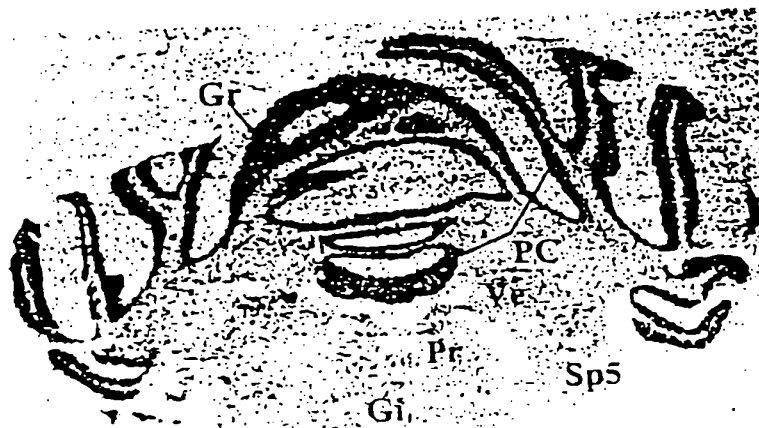


FIGURE 19G

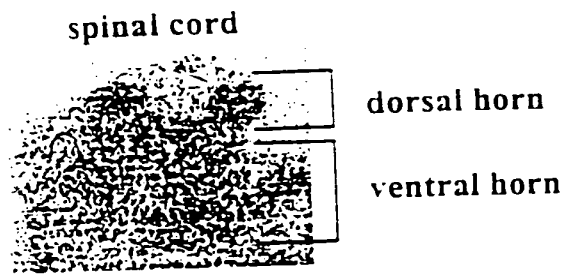


FIGURE 19H

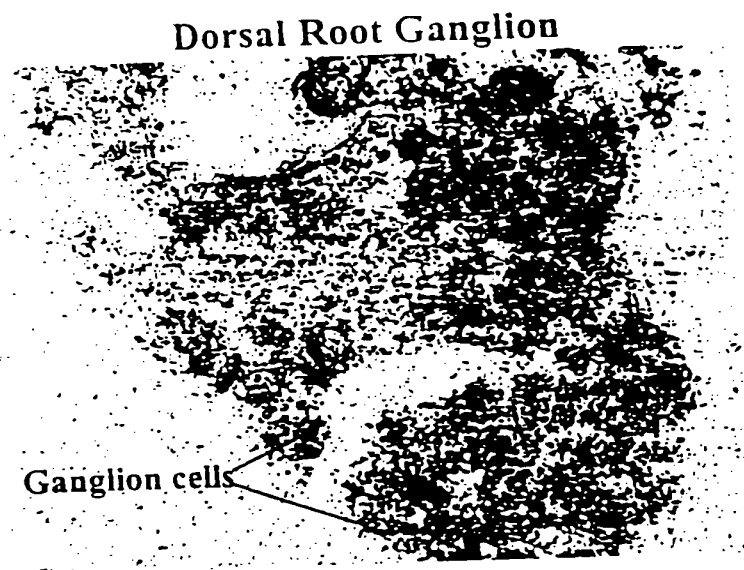


FIGURE 19I

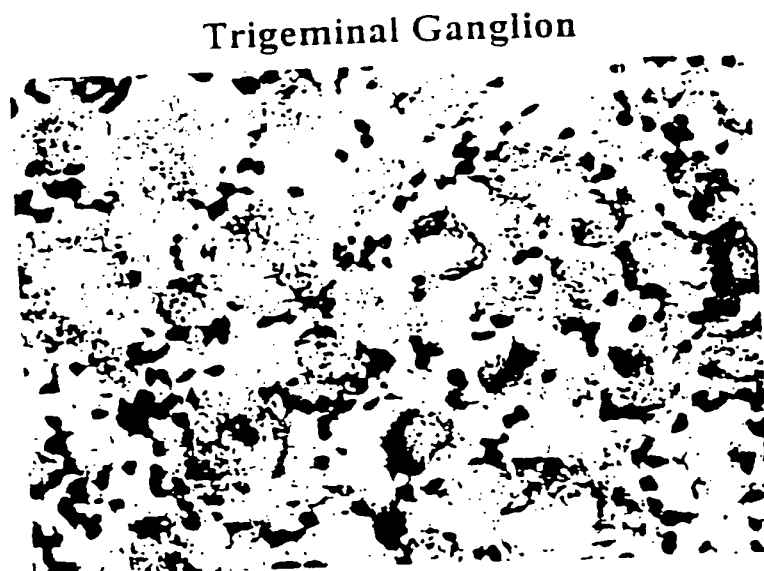


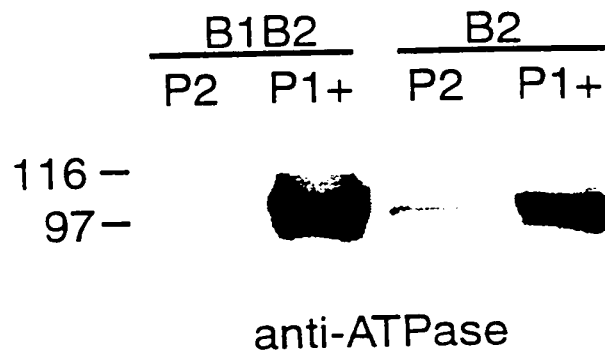
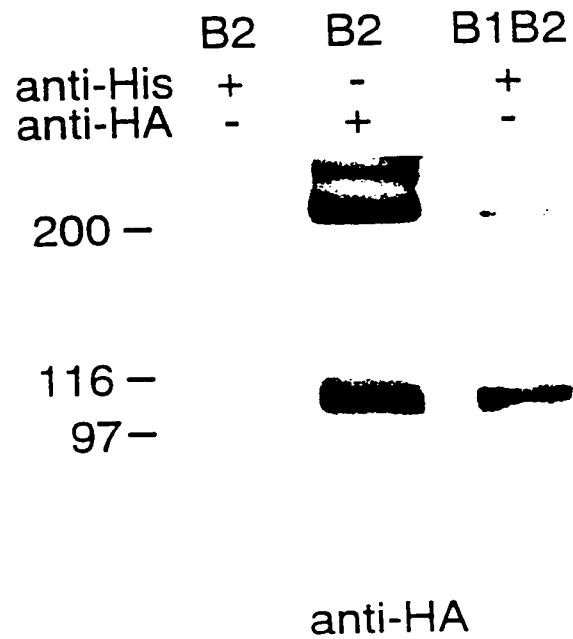
Figure 20A**Figure 20B**

Figure 20C

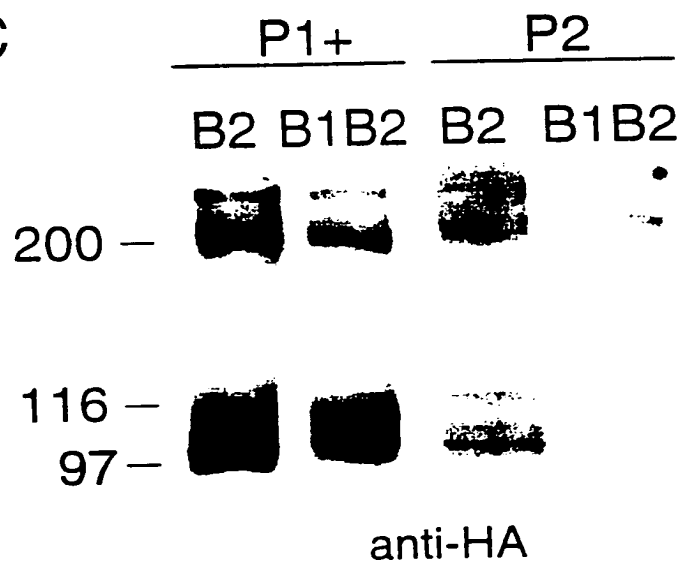


Figure 21A



Figure 21B



Figure 21C



Figure 21D



Figure 21E

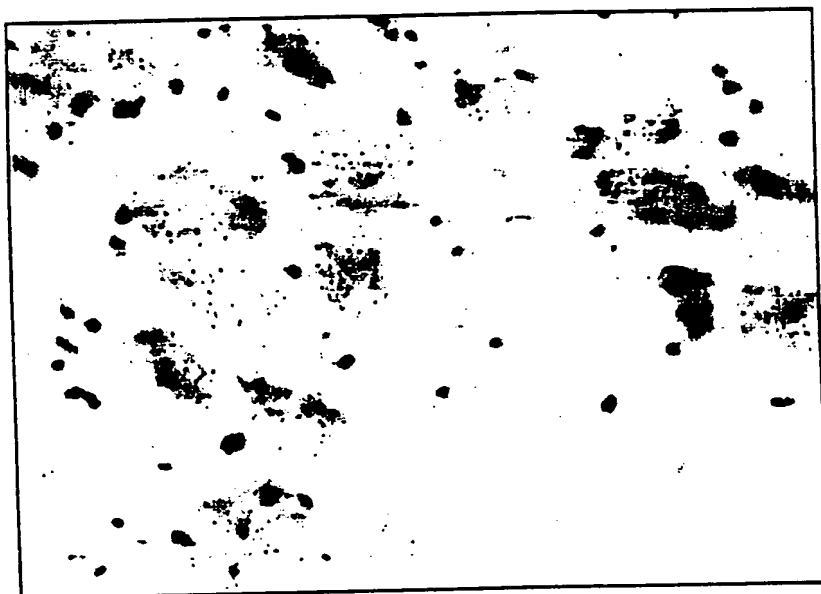


Figure 21F



FIGURE 22A

1 ATGGCTTCCCCGGGAGCTCCGGGGCAGCCCCGGGCCCGCCCGCCGCCACCGCCGCCCC 60
61 GCGCGCCTGCTACTGCTACTGCTGCTGCCGCTGCTGCTGCCCTCTGGCGCCCCGGGCTTG 120
121 GGCTGGGCGGGGGCCCCCCCCGGGCCGCCAGCAGCCCCGCGCTCTCCATCATGGGC 180
181 CTCATGCCCCGCTCACCAAGGAGGTGGCCCAAGGGCAGCATCGGGGCGGGTGTGCTCCCCCGCC 240
241 GTGGAACCTGGCCATCGAGCAGATCCGCAACGAGTCACTCTGCGCCCCCTACTTCCCTCGAC 300
301 CTGCGGCTCTATGACACGGAGTGCGACAAACGCAAAAGGGTTGAAAGCCTTCTACGATGCG 360
361 ATAAAATACGGGCCGAACCACTTGATGGTGTGGAGGCGTCTGTCCATCCGTCACATCC 420
421 ATCATTCAGAGTCCCCTCCAAGGCTGGAATCTGGTGCAGCTTCTTTTGTGCTGCAACCACG 480
481 CCTGTTCTAGCCGATAAGAAAAAATAACCCCTTATTTCTTCGGACCGTCCCATCAGACAAT 540
541 GCGGTGAATCCAGCCATCTGAAGTTGCTCAAGCACTACCAGTGGAAGCGGTGGGCACG 600
601 CTGACGCAAGACGTTACAGAGGTTCCTCTGAGGTGCGGAATGACCTGACTGGAGTTCTGTAT 660
661 GCGGAGGACATTGAGATTTCAGACACCGAGAGCTTCTCCAACGATCCCTGTACCAGTGTC 720
721 AAAAAGCTGAAGGGGAATGATGTGCGGATCATCCTTGGCCAGTTTGACCAGAAATATGGCA 780
781 GCAAAAGTGTCTGTGTCATACGAGGAGAACATGTATGGTAGTAAATATCAGTGGATC 840

FIGURE 22B

841	ATTCCGGGCTGGTACGAGCCTTCTTGGTGGGAGCAGGTGCACACGGAAGCCAACTCATCC	900
901	CGCTGCCCTCCGGAAGAATCTGCTTGTCTGCCATGGAGGGCTACATTGGCGTGGATTTCGAG	960
961	CCCCTGAGCTCCAAGCAGATCAAGACCATCTCAGGAAAGACTCCACAGCAGTATGAGAGA	1020
1021	GAGTACAACAACAAGCGGTTCAGGCGTGGGGCCCCAGCAAGTTCCACGGGTACGCCCTACGAT	1080
1081	GGCATCTGGGTTCATCGCCCAAGACACTGCAGAGGGCCCATGGAGACACTGCATGCCAGCAGC	1140
1141	CGGCACCAGCGGATCCAGGACTTCAACTACACGGACCACACGCTGGCAGGATCATCCCTC	1200
1201	AATGCCATGAACGAGACCAACTTCTTCGGGGTACGGGTCAAGTTGTATTCGGAATGGG	1260
1261	GAGAGAAATGGGGACCAATTAAATTTACTCAATTTCAAGACACAGCAGGGAGGTGAAGGTGGGA	1320
1321	GAGTACAACGCTGTGGCCGACACACTGGAGATCATCAATGACACCATCAGGTTCCAAAGGA	1380
1381	TCCGAACCAACCAAAAGACAAGACCATCATCTCTGGAGCAGCTGCCGGAAGATCTCCCCTACCT	1440
1441	CTCTACAGCATCCTCTCTGCCCCTCACCATCCTCGGGATGATCATGGCCAGTGCTTTTCTC	1500
1501	TTCTTCAACATCAAGAACCAGGAATCAGAAGCTCATAAAGATGTCGAGTCCCATACATGAAC	1560
1561	AACCTTATCATCCTTGGAGGGATGCTTTCCCTATGCTTCCATATTTCTCTTTGGCCCTTGAT	1620
1621	GGATCCTTTGTCTCTGAAAAGACCTTTTGAAACACTTTGCACCGTCAGGACCTGGATTCTC	1680

FIGURE 22C

1681 ACCGTGGGCTACACGACCGCTTTTGGGGCCATGTTTGCAAAGACCTGGAGAGTCCACGCC 1740
 1741 ATCTTCAAAAATGTGAAAATGAAGAAGAAGATCATCAAGGACCAGAAAACCTGCTTGTGATC 1800
 1801 GTGGGGGCATGCTGCTGATCGACCTGTGTATCCTGATCTGCTGGCAGGCTGTGGACCCC 1860
 1861 CTGCGAAGGACAGTGGAGAAAGTACAGCATGGAGCCGACCCAGCAGGACGGGATATCTCC 1920
 1921 ATCCGCCCTCTCCTGGAGCACTGTGAGAAACACCCATATGACCATCTGGCTTGGCATCGTC 1980
 1981 TATGCCCTACAAGGGACTTCTCATGTGTGTTTCGGTTGTTTCTTAGCTTGGGAGACCCGCAAC 2040
 2041 GTCAGCATCCCCCGCACTCAACGACAGCAAGTACATCGGGATGAGTGTCTACAAACGTGGGG 2100
 2101 ATCATGTGCATCATCGGGGCCGCTGTCTCCTTCTGTACCCCGGACCAAGTGTGCAG 2160
 2161 TTCTGCATCGTGGCTCTGGTCATCATCTTCTGCAGCACCATCACCCCTCTGCCCTGGTATTC 2220
 2221 GTGCCGAAGCTCATACCCCTGAGAAACAAACCCAGATGCAGCAACGCAGAACAGCGGATTC 2280
 2281 CAGTTCACTCAGAAATCAGAAAGAAAGAGATTCTAAAACGTCCACCTCGGTCAACCAGTGTG 2340
 2341 AACCAAGCCAGCACATCCCGCCTGGAGGGCCTACAGTCAGAAAACCATCGCCTGCCAATG 2400
 2401 AAGATCACAGAGCTGGATAAAGACTTGGAAGAGGTCAACCATGCAGCTGCAGGACACACCA 2460
 2461 GAAAAGACCCTACATTAAACAGAACCACTACCAAGAGCTCAATGACATCCTCAACCTG 2520

FIGURE 22D

2521	GGAAACTTCACTGAGAGCACAGATGGAGGAAAGGCCATTTTAAAAAATCACCTCGATCAA	2580
2581	AATCCCCAGCTACAGTGGAAACAACAGAGCCCTCTCGAACATGCAAGATCCTATAGAA	2640
2641	GATATAAACTCTCCAGAACACATCCAGCGTCGGCTGTCCCTCCAGCTCCCCCATCCTCCAC	2700
2701	CACGCCCTACCTCCCATCCATCGGAGGCGTGGACGCCAGCTGTGTCAAGCCCCCTGCGTCAGC	2760
2761	CCCACCGCCAGCCCCCGCCACAGACATGTGCCACCCCTCCTTCCGAGTCATGGTCTCGGGC	2820
2821	<u>CTGTAA</u>	2826

FIGURE 23A

[illegible]

FIGURE 23B

281	I	P	G	W	Y	E	P	S	W	E	Q	V	H	T	E	A	N	S	S	300	
301	R	C	L	R	K	N	L	L	A	A	M	E	G	Y	I	G	V	D	F	E	320
321	P	L	S	S	K	Q	I	K	T	I	S	G	K	T	P	Q	Q	Y	E	R	340
341	E	Y	N	N	K	R	S	G	V	G	P	S	K	F	H	G	Y	A	Y	D	360
361	G	I	W	V	I	A	K	T	L	Q	R	A	M	E	T	L	H	A	S	S	380
381	R	H	Q	R	I	Q	D	F	N	Y	T	D	H	T	L	G	R	I	I	L	400
401	N	A	M	N	E	T	N	F	F	G	V	T	G	Q	V	V	F	R	N	G	420
421	E	R	M	G	T	I	K	F	T	Q	F	Q	D	S	R	E	V	K	V	G	440
441	E	Y	N	A	V	A	D	T	L	E	I	I	N	D	T	I	R	F	Q	G	460
461	S	E	P	P	K	D	K	T	I	I	L	E	Q	L	R	K	I	S	L	P	480
481	L	Y	S	I	L	S	A	L	T	I	L	G	M	I	M	A	S	A	F	L	500
501	F	F	N	I	K	N	R	N	Q	K	L	I	K	M	S	S	P	Y	M	N	520
521	N	L	I	I	L	G	G	M	L	S	Y	A	S	I	F	L	F	G	L	D	540
541	G	S	F	V	S	E	K	T	F	E	T	L	C	T	V	R	T	W	I	L	560

FIGURE 23C

561	T	V	G	Y	T	T	A	F	G	A	M	F	A	K	T	W	R	V	H	A	580
581	I	F	K	N	V	K	M	K	K	K	I	I	K	D	Q	K	L	L	V	I	600
601	V	G	G	M	L	L	I	D	L	C	I	L	I	C	W	Q	A	V	D	P	620
621	L	R	R	T	V	E	K	Y	S	M	E	P	D	P	A	G	R	D	I	S	640
641	I	R	P	L	L	E	H	C	E	N	T	H	M	T	I	W	L	G	I	V	660
661	Y	A	Y	K	G	L	L	M	L	F	G	C	F	L	A	W	E	T	R	N	680
681	V	S	I	P	A	L	N	D	S	K	Y	I	G	M	S	V	Y	N	V	G	700
701	I	M	C	I	I	G	A	A	V	S	F	L	T	R	D	Q	P	N	V	Q	720
721	F	C	I	V	A	L	V	I	I	F	C	S	T	I	T	L	C	L	V	F	740
741	V	P	K	L	I	T	L	R	T	N	P	D	A	A	T	Q	N	R	R	F	760
761	Q	F	T	Q	N	Q	K	K	E	D	S	K	T	S	T	S	V	T	S	V	780
781	N	Q	A	S	T	S	R	L	E	G	L	Q	S	E	N	H	R	L	R	M	800
801	K	I	T	E	L	D	K	D	L	E	E	V	T	M	Q	L	Q	D	T	P	820
821	E	K	T	T	Y	I	K	Q	N	H	Y	Q	E	L	N	D	I	L	N	L	840

FIGURE 23D

841	G	N	F	T	E	S	T	D	G	G	K	A	I	L	K	N	H	L	D	Q	860
861	N	P	Q	L	Q	W	N	T	T	E	P	S	R	T	C	K	D	P	I	E	880
881	D	I	N	S	P	E	H	I	Q	R	R	L	S	L	Q	L	P	I	L	H	900
901	H	A	Y	L	P	S	I	G	G	V	D	A	S	C	V	S	P	C	V	S	920
921	P	T	A	S	P	R	H	R	H	V	P	P	S	F	R	V	M	V	S	G	940
941	L																			941	